ing of the target RNA by endogenous ADAR because of the double stranded nature of the target RNA and the oligonucleotide hybridizing thereto. The oligonucleotides of Woolf et al. (1995) that were 100% complementary to the target RNA sequences only appeared to function in cell extracts or in amphibian (*Xenopus*) oocytes by microinjection, and suffered from severe lack of specificity: nearly all adenosines in the target RNA strand that was complementary to the antisense oligonucleotide were edited. An oligonucleotide, 34 nucleotides in length, wherein each nucleotide comprised a 2'O-methyl modification, was tested and shown to be inactive in Woolf et al. (1995). In order to provide stability against nucleases, a 34-mer RNA, modified with 2'O-methyl-modified phosphorothioate nucleotides at the 5'- and 3'-terminal 5 nucleotides, was also tested. It was shown that the central unmodified region of this oligonucleotide could promote editing of the target RNA by endogenous ADAR, with the terminal modifications providing protection against exonuclease degradation. Woolf et al. (1995) does not achieve deamination of a specific target adenosine in the target RNA sequence. As mentioned, nearly all adenosines opposite an unmodified nucleotide in the antisense oligonucleotide were edited (therefore nearly all adenosines opposite nucleotides in the central unmodified region, if the 5'- and 3'-terminal 5 nucleotides of the antisense oligonucleotide were modified, or nearly all adenosines in the target RNA strand if no nucleotides were modified). It is known that ADAR may act on any dsRNA. Through a process sometimes referred to as 'promiscuous editing', the enzyme will edit multiple A's in the dsRNA. Hence, there is a need for methods and means that circumvent such promiscuous editing and that only target specified adenosines in a target RNA sequence for therapeutic applicability. Vogel et al. (2014) showed that such off-target editing can be suppressed by using 2'-O-methyl-modified nucleotides in the oligonucleotide at positions opposite to the adenosines that should not be edited, and use a non-modified nucleotide directly opposite to the specifically targeted adenosine on the target RNA. However, the specific editing effect at the target nucleotide has not been shown to take place in that article without the use of recombinant ADAR enzymes that have covalent bonds with the antisense oligonucleotide.

[0009] It is noted that yet another editing technique exists which uses oligonucleotides, known as the CRISPR/Cas9 system. However, this editing complex acts on DNA. It also suffers from the same drawback as the engineered ADAR systems described above, because it requires co-delivery to the target cell of the CRISPR/Cas9 enzyme, or an expression construct encoding the same, together with the guide oligonucleotide.

[0010] In view of the above, there remains a need for new techniques and compounds that can utilise endogenous cellular pathways and naturally available ADAR enzymes to specifically edit endogenous nucleic acids in mammalian cells, even in whole organisms, without the problems associated with the methods of the prior art.

SUMMARY OF THE INVENTION

[0011] The present invention does away with the drawbacks of the methods according to the prior art by providing a targeted approach to RNA editing using, in one embodiment, an antisense oligonucleotide (AON) capable of forming a double stranded complex with a target RNA in a cell, for the deamination of a specific target adenosine in said target RNA by a mammalian ADAR enzyme present in said cell; wherein said AON is complementary to a target RNA comprising the target adenosine, said AON optionally comprising one or more mismatches, wobbles and/or bulges with said target RNA; wherein the AON comprises one or more nucleotides with a sugar modification, provided that the nucleotide opposite the target adenosine comprises a ribose with a 2'-OH group or a deoxyribose with a 2'-H group; wherein the AON does not comprise a (non-complementary) portion (non-complementary to the target and non-complementary in respect of itself) that is capable of forming an intramolecular stem-loop structure that is capable of binding a mammalian ADAR enzyme; wherein the AON does not include a 5'-terminal O6-benzylguanine or a 5'-terminal amino modification; and wherein the AON is not covalently linked to a SNAP-tag domain. The AON of the present invention is preferably in its basic structure a single-stranded RNA-editing oligonucleotide. In a preferred embodiment, the nucleotide opposite the target adenosine is a cytidine or a uridine, more preferably a cytidine. In yet another preferred aspect, the nucleotide directly 5' and/or 3' from the nucleotide opposite the target adenosine comprise a ribose with a 2'-OH group, or a deoxyribose with a 2'-H group. To prevent degradation by endonucleases as much as possible, preferably all other nucleotides in said AON besides the nucleotide that is opposite the target adenosine and one or both of the nucleotides directly adjacent to the opposing nucleotide comprise a 2'-O-alkyl group, preferably a 2'-O-methyl group. In another preferred aspect, each nucleotide that is opposite an adenosine in the target RNA sequence comprises a 2'-O-alkyl group, preferably a 2'-O-methyl group, except for the nucleotide opposite the target adenosine, which comprises a ribose with a 2'-OH group. In yet also a preferred embodiment, the AON comprises, besides the cytidine opposite the target adenosine (which may the single mismatch) at least one additional mismatch or wobble base pair with the target sequence. The presence of the at least one additional mismatch and/or wobble base pair may add to the RNA editing efficiency possibly because it adds to the altered on/off rate of the AON with its target molecule and/or to the binding and/or recognition of the ADAR molecule to the dsRNA, also depending on the target sequence. As outlined herein, one particular preferred position for an additional mismatch and/or wobble base pair between AON and target sequence (besides the preferred C-A of the target position) is the position at four nucleotides upstream (towards 5') of the target adenosine in the target sequence. It is also disclosed herein that, depending on the target sequence, additional mismatches and/or wobble base pairs, as well as additional bulges (non-pairing and small out-looping stretches of nucleotides) may add to the RNA editing efficiency. It is therefore a preferred aspect of the present invention to have additional bulges, mismatches and/or wobbles between the AON and the target sequence, besides the difference between the cytidine opposite the target adenosine (or besides the uridine opposite the target adenosine, which is then not a mismatch but which may be preferred for certain target sequences). In a preferred aspect the cell in which the AON is introduced is a human cell. In yet another preferred aspect the AON of the present invention comprises at least one phosphorothioate linkage, preferably wherein the 2, 3, 4, 5, or 6 terminal nucleotides of the 5' and 3' terminus of the AON are linked with phosphoro-